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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,674	OI ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) *32-34* is/are withdrawn from consideration.

5)☒ Claim(s) *35,36 and 38-44* is/are allowed.

6)☒ Claim(s) *22-25 and 28* is/are rejected.

7)☒ Claim(s) *26 and 29-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Allowable subject matter*.

The Amendment and Response filed on January 20, 2004 is acknowledged. The amendments to the claims have been entered as requested. Claim 39 is canceled. New claim 44 has been added. Claims 22, 24, 27, 29, 30, 35, 41, and 42 are amended. Claims 22-38 and 40-44 are pending. Claims 32-35 are withdrawn from examiner's consideration as drawn to the nonelected invention. Claims 22-31, 36-38 and 40-44 are the subject of this Office Action.

Detailed Office Action

1. Objections

1.1. Oath

The objection to the oath is withdrawn because the supplemental declaration has been filed.

1.2. Claims

Claims 29 and 41 are objected to for use of the term "a protein portion". This is not a standard term in the art. Please replace in claims 29 and 41 the term "a protein portion" with "a fragment".

2. Restriction/election

In the previous Office Action mailed Sept. 16, '03, the examiner issued the restriction requirement quoted below.

"Newly submitted claims 32, 33 and 34 are directed to an invention that is independent or distinct from the invention originally elected, because the Applicant elected, in paper No. 7, filed on Nov. 4, 2002, to prosecute claims 1-6 and 8-13 directed to DNA of SEQ ID NO: 4 encoding protein of SEQ ID NO: 3. The newly filled claims 22-43 are directed to the following inventions:

I. Claim 22-31 and 35-43, drawn to isolated nucleic acid of SEQ ID NO: 4 or encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, expression vector, host cell and the method of producing polypeptides that comprises SEQ ID NO: 3 classified in class 435, subclass 212.

II. Claim 32, 33 and 34, all in part, drawn to SEQ ID NO: 24, classified in class 536, subclass 23.2.

III. Claim 32 and 33 both in part, drawn to SEQ ID NO: 26, classified in class 536, subclass 23.2.

IV. Claim 32, 33 and 34, all in part, drawn to SEQ ID NO: 28, classified in class 536, subclass 23.2.

V. Claim 32 and 33,both in part, drawn to SEQ ID NO: 30, classified in class 536, subclass 23.2.

VI. Claim 32, 33 and 34, all in part, drawn to SEQ ID NO: 34, classified in class 536, subclass 23.2.

VII. Claim 32 and 33, both in part, drawn to SEQ ID NO: 36, classified in class 536, subclass 23.2.

VIII. Claim 32,33 and 34, all in part, drawn to SEQ ID NO: 38, classified in class 536, subclass 23.2.

IX. Claim 32 and 33, both in part, drawn to SEQ ID NO: 40, classified in class 536, subclass 23.2.

Inventions I-IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions, DNA molecules of SEQ ID NO: 4, 24, 26, 28, 30, 34, 36, 38, and 40 are divergent molecules having different chemical structures. As to their enzymatic activities, Applicants provided an evidence that DNA of SEQ ID NO: 4 encodes protein of SEQ ID NO: 3 having the activity of dipeptidyl peptidase. This, however, does not mean that polypeptides encoded by SEQ ID NO: 24, 26, 28, 30, 34, 36, 38, and 40 have the same enzymatic activity as the polypeptide encoded by SEQ ID NO: 3, because although these DNA molecules are splice variants of the same primary transcript of undisclosed genomic sequence, the proteins they encode may have different biological functions and effects. In addition, SEQ ID NO: 4, 24, 26, 28, 30, 34, 36, 38, and 40 are not disclosed as capable of use together. For these reasons the restriction between Groups I-IX is proper.

The Applicant elected, in paper No. 7, filed on Nov. 4, 2002, to prosecute original claims 1-6 and 8-13 directed to DNA of SEQ ID NO: 4 encoding protein

of SEQ ID NO: 3. [It is emphasized that the restriction of the original claims 1-21 required the election between 18 inventions, i.e. six invention related to the enzymes of SEQ ID NOs: 1, 3, and 5. Claims 1-21 were deleted in response to the First Office Action on Merits]. Applicant has received an action on the merits for the originally presented invention; this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 32, 33 and 34 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03."

Traversing this restriction in their current response Applicants write on page 6:

"Claim 6 that was elected read as follows:

6. The isolated nucleic acid of claim 1 which is an alternative splice variant of one of SEQ I NOS: 2, 4, and 6.

Claims 32, 33, and 34, which presently stand withdrawn, recite, in varying degrees of specificity, alternative splice variants of SEQ ID NO: 4. Thus, it is submitted that these claims are not 'independent and distinct from the invention originally elected'; they are clearly a part of the invention originally elected."

Applicants' arguments have been fully considered but are found not persuasive for the following reasons. Claim 6 is generic. The genus of alternative splice variants of SEQ ID NO: 4 is the genus of species that are independent of SEQ ID NO: 4. SEQ ID NOS: 24, 26, 28, 30, 34, 36, and 38 are independent and distinct because their

structure/function is distinct. One skilled in the art is unable to predict how the primary transcript of the gene encoding DPRP2 will be actually spliced, and how the alternative splicing will influence the function of the translated protein. Applicants argue, see page 7, line 11 of the REMARKS, that all the alternative DNA splice variants code polypeptides that would have propyl oligopeptidase activity. This however is not true, because although most of alternative splice variants are likely to remain active, SEQ ID NO: 25 lacks the active center consisting of amino acids GWSYG and for that reasons cannot be active. Applicants teach that the genomic DNA of DPR2 consists of 27 exons. Theoretical number of alternative splice variants of the primary transcript of such gene is 2^{26}, which is more than a million. Although not all of the possible permutations of exons and introns exist in nature, there is no evidence that the nine alternative splice variants of the primary transcript disclosed by Applicants are the only ones that exist.

In conclusion, because the generic term "splice variants" does not anticipate its species, SEQ ID NO: 4 and 24, 26, 28, 30, 34, 36, and 38 are independent products having different structures/functions and because SEQ ID NO: 24, 26, 28, 30, 34, 36, and 38 were not claimed in the claims as originally filed, restriction as issued in the last Office Action is proper and MADE FINAL. Claims 32-34 remain withdrawn from consideration as drawn to the nonelected invention; see 37 CFR 1.141(b).

3. Rejections

3.1. 35 U.S.C. 112, second paragraph

Rejection of claims 22-31, 35-43 under 35 U.S.C. 112, second paragraph, made in the Office Action of September 16, 2003 is withdrawn because the claims have been amended.

New rejection

Claim 22 is confusing, because of the recitations "the same biological function" and "prolyl oligopeptidase activity". The term "the same biological function" is generic. The scope of the term includes biological functions not related to "prolyl oligopeptidase activity', for example a function of inducing antibodies.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 22 recites the broad recitation "the same biological function", and the claim also recites "prolyl oligopeptidase activity" which is the narrower statement of the range/limitation.

For examination purposes it is assumed that the term "the same biological function" means "prolyl oligopeptidase activity".

Claims 24 and 25 are confusing because of the terms "DNA transcript" in claim 24 and "the DNA" in claim 25.

A DNA transcript is RNA. Thus claim 25 cannot recite in the second line the DNA. Please replace "DNA transcript" with "RNA" in claim 24 and "the DNA" with "the RNA" in claim 25 or replace "DNA transcript" with "DNA fragment".

3.2. 35 USC section 112, first paragraph

3.2.1. Lack of written description

Rejection withdrawal

Rejection of claims 29, 30, 31 and 41-43 under 35 U.S.C. 112, first paragraph made in the first Office Action, because "a mature portion of the amino acid sequence of SEQ ID NO: 3" is lacking written description is withdrawn because the claims have been amended.

New rejection

Claims 25 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 is directed to an antisense oligonucleotide directed against the transcript of DNA molecule that includes the entire length of SEQ ID NO: 4, or which is complementary to the entire coding region of SEQ ID NO:4.

Claim 37 is directed to an antisense oligonucleotide directed against isolated nucleic acid which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:3, a fragment thereof which exhibits prolyl oligopeptidase, or which is complementary thereto.

The claims are directed to a large genus of antisense molecules the structure and function of which is not sufficient described in the claims or specification. Applicants teach two representative species of said genus, i.e. the DNA which is complementary to SEQ ID NO:4 or RNA that a is full length transcript of SEQ ID NO:4. These two molecules have identified structure and function, because when used as an antisense nucleic acid they prevent expression of DNA of SEQ ID NO: 4. The specification fails to describe any other representative species of the antisense oligonuclotides by any identifying characteristics. In view of lack of functional and structural characteristics of claimed antisense nucleotides, Applicants failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention.

To overcome this rejection the examiner suggests the following language for claims 25 and 37.

Claim 25. An antisense oligonucleotide comprising fragment DNA of claim 24 wherein said fragment inhibits expression of prolyl oligopeptidase.

Claim 37. An antisense oligonucleotide comprising a fragment of DNA of claim 35 wherein said fragment inhibits expression of prolyl oligopeptidase.

3.2.2. *Scope of enablement*

Claim 22, 23, 25, 28 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 4 encoding SEQ ID NO: 3 or for a DNA molecule encoding a fragment of SEQ ID NO: 3 having prolyl oligopeptidase activity, does not reasonably provide enablement for any

1) isolated nucleic acid encoding a polypeptide comprising an amino acid sequence that is at least 90% similar to SEQ ID NO: 3 or

2) isolated nucleic acid encoding a fragments of a polypeptide comprising an amino acid sequence that is at least 90% similar to SEQ ID NO: 3,

wherein polypeptides encoded by 1) and 2) exhibit prolyl oligopeptidase activity.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of polynucleotides covered by subgenera (1) and (2). See also the above rejection for lack of written description.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered

in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any polynucleotide, natural or man-made,

1) encoding a polypeptide comprising an amino acid sequence that is at least 90% similar to SEQ ID NO: 3 or

2) encoding a fragments of a polypeptide comprising an amino acid sequence that is at least 90% similar to SEQ ID NO: 3,

wherein polypeptides encoded by 1) and 2) exhibit prolyl oligopeptidase activity.

While methods of gene cloning and gene structure manipulations are well known in the relevant art, and skills of the artisans highly developed, no one is able to make any polynucleotide enumerated under (1) – (2) above, because the lack of structural characteristics of said polynucleotides makes the probability of success in obtaining the claimed invention low.

While enablement is not precluded by the necessity for routine gene manipulation and screening expressed polypeptides of required function, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so

that the claimed species have the functionality of prolyl oligopeptidase. The provision of SEQ ID NO: 4 fails to provide such guidance of polynucleotides with major structural variations therefrom which remain encompassed within the scope of the rejected claims.

Without a further guidance on the part of Applicants with regards to the structure of the claimed inventions experimentation left to those in the art is improperly extensive and undue.

3.2. 35 USC section 102

Rejection of claims 22-23, 28, 35-36 and 40, made in the Office Action of September 16, 2003 under 35 U.S.C. 102(e), as being anticipated by the US Patent No. 6,569,662 is withdrawn because the actual sequence listing of the patent that contains 1105 sequences does not contain SEQ ID NO: 99 that is 2801 nucleotides long and encodes a protein that is in 94.3% similar to SEQ ID NO: 3.

4. Conclusion

Claims 22-15 and 28 are rejected. Claims 26-27, 29-31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 35-36 and 38-44 are allowed. The following is the examiner's reason for indicating allowable subject matter.

Applicants disclose a novel DNA molecule encoding the new human prolyl oligopeptidase of SEQ ID NO:3. The enzyme belongs to the family of serine proteases called DPPIV that are involved in numerous physiological processes, specifically in diabetes. Inhibitors of the newly disclosed enzyme are potentially usefull in clinics.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0928. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (572) 272-0928. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner